Original Article

Description of Baseline Characteristics of Pediatric Allergic Asthma Patients Including those Initiated on Omalizumab

Allergy & Rhinology
Volume 9: 1–9

DOI: 10.1177/2152656718763387
journals.sagepub.com/home/aar
SAGE

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Abstract

Background: Indication of omalizumab in the United States was recently extended to include pediatric (6–11 years) uncontrolled moderate-to-severe allergic asthma patients.

Objective: The purpose of this study was to describe baseline characteristics of this population from a real-world dataset.

Methods: Allergic asthma patients and uncontrolled moderate-to-severe allergic asthma patients, aged 6–11 years, were identified in the Allergy Partners Network Electronic Medical Records (2007–2016). The index date for allergic asthma patients was the latest between the second asthma-related visit and the allergic status confirmation. Uncontrolled moderate-to-severe allergic asthma patients were stratified into omalizumab-exposed (index date) or omalizumab-unexposed (index date randomly generated) groups. Characteristics were evaluated during the 12-month preindex period.

Results: A total of 5806 allergic asthma, 37 omalizumab-exposed, and 2620 omalizumab-unexposed patients were selected (mean age approximately 9 years). Allergic asthma and omalizumab-unexposed patients were predominantly white (70.2% and 61.2%) whereas the majority of omalizumab-exposed were African Americans (62.2%). Mean immunoglobulin E was 782.0 IU/ml in allergic asthma patients (available in 2.2%), 1134.4 IU/ml in omalizumab-exposed (available in 100.0%), and 746.1 IU/ml in omalizumab-unexposed (available in 3.1%). Allergic asthma patients were less severe than omalizumab-exposed and omalizumab-unexposed based on the forced expiratory volume in 1 s as a percentage of predicted value (FEV_1% predicted) and the Childhood Asthma Control Test (C-ACT). FEV_1% predicted was below normal (<80%) in 42.4% of omalizumab-exposed and 39.1% of omalizumab-unexposed patients, also 63.6% of omalizumab-exposed and 46.7% of omalizumab-unexposed had uncontrolled asthma (C-ACT score <20). In African American omalizumab-exposed patients, FEV_1% predicted was below normal in 47.6% and 55.0% had uncontrolled asthma.

Conclusions: In a real-world setting, pediatric patients with uncontrolled moderate-to-severe allergic asthma have a significant disease burden as shown by high rates of poor lung function, disease control, and symptoms. Currently available treatments could help improve disease management in this population.

Keywords

allergic asthma, moderate-to-severe asthma, uncontrolled asthma, omalizumab, anti-immunoglobulin E antibody, biologic, pediatric asthma, electronic medical records, baseline characteristics, clinical profile

Introduction

Asthma is one of the most widespread and disabling chronic conditions in children.[1] In the United States, its estimated prevalence in children is 9.6%.[2] While severe asthma exacerbations frequently require a hospital admission or intensive care, asthma is also often associated with difficulty sleeping, reduction in physical activities, school absenteeism, and decline of school performance.[1,3–6]

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Early allergic sensitization is a major risk factor for persistent asthma, and severe asthma is associated with being highly allergic in children.[7,8] Although approximately 5% of children suffer from severe asthma, it accounts for almost 50% of asthma-related costs and most of the asthma-related morbidity.[9,10]

Treatment of moderate-to-severe asthma in children could be challenging. The mainstay therapy is higher dose inhaled corticosteroids (ICS) in combination with long-acting beta2-agonist (LABA) and other add-on medications if asthma remains uncontrolled.[11,12] However, higher doses of ICS increase the risk of adverse events, and some of them (e.g., short stature) could be different from those occurring in adults.[13–15] Moreover, plateau in efficacy is observed with increasing doses of ICS.[16,17] This significantly shifts the benefit-risk profile of high-dose ICS in pediatric patients. In allergic asthma (AA), an additional, nonpharmacological aspect of treatment could be allergen avoidance.[18,19]

Omalizumab, a monoclonal antibody binding to free serum immunoglobulin E (IgE), is used in moderate-to-severe AA which is not well controlled on ICS.[20,21] In July 2016, an expanded age range including children aged 6–11 years was approved for omalizumab in the U.S. Clinical trials have demonstrated that omalizumab as an add-on to current asthma therapy is effective and adequately tolerated in pediatric patients.[22,23] However, due to the recent approval, data on characteristics of pediatric patients receiving omalizumab in the U.S. clinical practice is scarce.

This study used electronic medical records (EMRs) data containing clinical characteristics such as total IgE level, asthma-related symptoms, asthma control, and lung function to describe the baseline profile of pediatric AA patients seen at the largest single specialty asthma, allergy, and immunology practice in the U.S. Given the context of the recently extended age indication of omalizumab in the U.S., baseline characteristics of moderate-to-severe AA patients with uncontrolled symptoms, exposed, and unexposed to omalizumab were also described.

Methods

Data Source

The Allergy Partners Network longitudinal EMR data (2007–2016) was used. The network is the largest U.S. practice specializing in allergic disease, asthma, and immunology. It consists of over 120 providers, spans over 20 states, and encompasses over 110 total locations of service.

Available data included patient demographics (age, sex, race, insurance type, and state), diagnoses (International Classification of Diseases, Clinical Modification, 9th (ICD-9-CM) and 10th (ICD-10-CM) revision codes, and physicians' description), prescription medications (Generic Product Identifier, generic and brand names, date of prescription start, strength and administration instructions), lung function measured as forced expiratory volume in 1 s as percentage of predicted value (FEV_1% predicted), laboratory test results (IgE, allergen sensitivities), Childhood Asthma Control Test™ (C-ACT) results, and caregiver-reported asthma-related symptoms. The study was exempted from Institutional Review Board review by the New England IRB.

Study Design

This retrospective EMR study described the baseline characteristics of three pediatric cohorts: AA cohort and two cohorts of moderate-to-severe AA patients with uncontrolled symptoms (omalizumab-exposed and omalizumab-unexposed cohorts).

The index date for the AA cohort was the latest between the date of the second asthma-related visit and the date when allergic status was confirmed. For the omalizumab-exposed cohort, the index date was the date of omalizumab initiation. For the omalizumab-unexposed cohort, a date mimicking the date of omalizumab initiation was randomly selected based on the distribution of time in the omalizumab-exposed cohort between omalizumab initiation and the latest of the two events: the first indicator of inadequately controlled symptoms or a test or diagnosis confirming patient's allergic status. Patient characteristics were measured as of the index date or over the 12 months prior to the index date defined as the baseline period.

Inclusion Criteria

To be included in the overall AA cohort, patients were required to have at least two asthma-related visits (ICD-9-CM: 493.xx; ICD-10-CM: J45.xxx) more than seven days apart, allergic status confirmed (defined below), 6–11 years of age as of the index date, and at least 12 months of preindex data. In addition, patients classified into omalizumab-exposed and omalizumab-unexposed cohorts were required to have moderate-to-severe asthma with uncontrolled symptoms (defined below). Exposure to omalizumab was defined based on whether or not a patient had a prescription for or an injection of omalizumab following an indicator of inadequately controlled symptoms. Omalizumab-exposed and omalizumab-unexposed cohorts were not exact subsets of the AA cohort due to the differences in index date.

Identification of Allergic Status. Allergic status was based on either a positive serum specific IgE test, a positive allergy skin test, a diagnosis of perennial allergic rhinitis

(ICD-9-CM: 477.8; ICD-10-CM: J30.89), or allergic rhinitis to animal hair or dander (ICD-9-CM: 477.2; ICD-10-CM: J30.81). Patients had to have their allergic status confirmed before the index date.

Identification of Moderate-to-Severe Asthma with Uncontrolled Symptoms. Moderate-to-severe asthma was identified based on either a diagnosis (ICD-10-CM: J45.4, J45.5 or physician's description) or treatments indicated for moderate-to-severe asthma (medium- to high-dose ICS with LABA or leukotriene receptor antagonist, theophylline, or zileuton).[11,12] Uncontrolled symptoms were identified based on C-ACT <20, FEV_1% predicted <80%, or initiation of oral corticosteroids (OCS) after the moderate-to-severe asthma status.

Measures of Asthma-Related Symptoms, Asthma Control, and Lung Function

Asthma-related symptoms of coughing, wheezing, shortness of breath, and chest tightness were measured during the baseline period using caregiver-reported information or as of the index date based on active problems identified with ICD-9-CM or ICD-10-CM codes.

Asthma control was measured based on the C-ACT, a patient-caregiver filled survey.[24,25] The C-ACT score ranging from 0 to 27 was reported as a continuous variable and as a set of categorical variables: well-controlled asthma (C-ACT $\geq$ 20), not well-controlled asthma (C-ACT 13-19), and very poorly controlled asthma (C-ACT $\leq$ 12).[25] C-ACT as of the last assessment during the baseline period was used.

Lung function was measured as FEV_1% predicted and reported as a continuous variable and as a categorical variable FEV_1% predicted <80%, defining a group of patients with lung function below normal. FEV_1% predicted as of the last assessment during the baseline period was used.

Statistical Analysis

Patient characteristics were described using mean, median, standard deviation, first quartile (Q1), third quartile (Q3), and interquartile range for continuous variables and frequencies and proportions for categorical variables. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Demographics

A total of 5806 AA, 37 omalizumab-exposed, and 2620 omalizumab-unexposed patients met the study inclusion criteria (Figure 1(a) and (b)). Mean age of AA patients was 8.6 years; among uncontrolled moderate-to-severe AA patients, mean age was 9.3 years in omalizumab-exposed and 9.0 years in omalizumab-unexposed (Table 1). The majority of AA (63.1%) and of uncontrolled moderate-to-severe AA patients were males; the proportion of males was lower in omalizumab-exposed (56.8%) compared to omalizumab-unexposed (61.8%) patients. AA and omalizumab-unexposed patients were predominantly white (70.2% and 61.2%, respectively) whereas omalizumab-exposed were African Americans (62.2%). The majority of AA (78.1%) and of uncontrolled moderate-to-severe AA patients had a private healthcare insurance plan; the proportion of patients with a private plan was lower and with a Medicaid plan higher in omalizumab-exposed compared to omalizumab-unexposed patients: (64.9% vs. 71.6% had a private plan; 32.4% vs. 25.5% had a Medicaid plan, respectively).

IgE and Asthma-Related Conditions

Mean total IgE was 782.0 IU/ml in AA patients (available in 2.2%). In omalizumab-exposed patients, it was higher (1134.5 IU/ml, available in 100.0%) than in omalizumab-unexposed (746.1 UI/ml, available in 3.1%; Table 1). Three of the most common asthma-related comorbidities included allergic rhinitis, atopic dermatitis, and food allergies. The prevalence of allergic rhinitis was 95.7% in AA patients; it was higher in omalizumab-exposed (100.0%) than in omalizumab-unexposed (96.5%) patients. Atopic dermatitis was present in 27.4% of AA patients, and its prevalence was also higher in omalizumab-exposed (45.9%) than in omalizumab-unexposed (30.1%) patients. The prevalence of food allergies was 28.6% in AA patients and similar in omalizumab-exposed (24.3%) and omalizumab-unexposed (26.3%) patients.

Asthma-Related Symptoms

During the baseline period, 41.7% of AA patients had coughing, 21.8% had wheezing, 21.0% had shortness of breath, and 10.0% had chest tightness. Among the two cohorts of uncontrolled moderate-to-severe AA patients, the omalizumab-exposed had a higher prevalence of symptoms (Figure 2). More specifically, comparing omalizumab-exposed to omalizumab-unexposed patients, 70.3% versus 47.2% had coughing, 56.8% versus 28.3% had wheezing, 54.1% versus 26.1% had shortness of breath, and 29.7% versus 15.0% had chest tightness.

Asthma Control and Lung Function

In AA patients, C-ACT score was <20 in 26.8%, and FEV_1% predicted was <80% in 23.9% (Table 1 and Figure 3). Based on C-ACT and FEV_1% predicted,

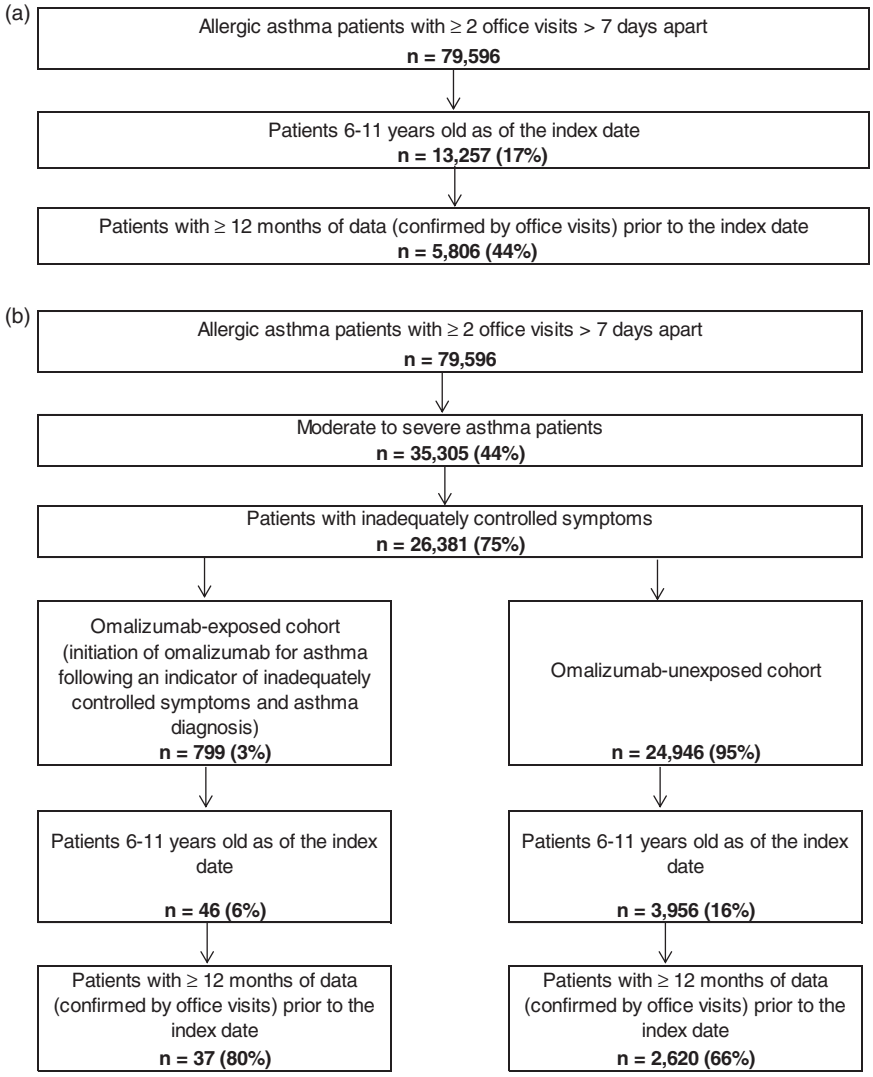

Figure 1. (a) Sample selection of pediatric allergic asthma patients. (b) Sample selection of pediatric moderate-to-severe allergic asthma patients with uncontrolled symptoms, omalizumab-exposed and omalizumab-unexposed cohorts.

omalizumab-exposed patients had a more severe profile among the two cohorts of uncontrolled moderate-to-severe AA patients. Comparing omalizumab-exposed to omalizumab-unexposed patients, C-ACT score was <20 in 63.6% versus 46.7%, and FEV1% predicted was <80% in 42.4% versus 39.1%. In omalizumab-exposed African American patients, C-ACT was <20 in 55.0% and FEV_1% predicted was <80% in 47.6% (data not shown).

Asthma-Related Medication Use

In AA patients, 44.3% received at least one ICS prescription, 1.3% were prescribed with high-dose ICS and LABA, and 6.5% with OCS (Table 1). Based on prescriptions, among the two cohorts of uncontrolled moderate-to-severe AA patients, omalizumab-exposed patients had a more severe profile. Comparing omalizumab-exposed to omalizumab-unexposed patients, 86.5% versus 70.9% received at least one ICS prescription, 37.8% versus 6.6% were prescribed with high-dose ICS and LABA, and 35.1% versus 20.9% with an OCS.

Discussion

This study offered new data on the profile of U.S. pediatric AA patients, including uncontrolled moderate-to-severe AA patients exposed and unexposed to omalizumab. Description of demographics and severity markers in pediatric AA overall provided the context for a better understanding of the uncontrolled moderate-to-severe disease. This benchmark could be useful to medical professionals and researchers and is a contribution of this study on its own to the literature on pediatric

Table 1. Patient Baseline Characteristics.

	Uncontrolled moderate-to-severe allergic asthma patients		
	Omalizumab-exposed n = 37	Omalizumab-unexposed n = 2620	Allergic asthma patients n = 5806
Demographics			
Age,[a] mean ± SD [median] (Q1–Q3, IQR)	9.32 ± 1.55 [10] (8–11, 3)	9.00 ± 1.58 [9] (8–10, 2)	8.61 ± 1.67 [9] (7–10, 3)
Female, n (%)	16 (43.2)	1001 (38.2)	2141 (36.9)
Race, n (%)			
White	14 (37.8)	1603 (61.2)	4078 (70.2)
Black or African American	23 (62.2)	719 (27.4)	1106 (19.0)
Other	0 (0.0)	56 (2.1)	141 (2.4)
Unknown	0 (0.0)	242 (9.2)	481 (8.3)
Healthcare insurance, n (%)			
Private	24 (64.9)	1876 (71.6)	4535 (78.1)
Medicaid	12 (32.4)	668 (25.5)	1123 (19.3)
Self-pay	1 (2.7)	27 (1.0)	54 (0.9)
Medicare	0 (0.0)	0 (0.0)	2 (0.0)
Unknown	0 (0.0)	49 (1.9)	92 (1.6)
Year of index date, n (%)			
2007	0 (0.0)	2 (0.1)	3 (0.1)
2008	0 (0.0)	40 (1.5)	50 (0.9)
2009	1 (2.7)	67 (2.6)	266 (4.6)
2010	3 (8.1)	144 (5.5)	653 (11.2)
2011	3 (8.1)	177 (6.8)	571 (9.8)
2012	5 (13.5)	259 (9.9)	896 (15.4)
2013	3 (8.1)	368 (14.0)	849 (14.6)
2014	6 (16.2)	319 (12.2)	844 (14.5)
2015	10 (27.0)	385 (14.7)	937 (16.1)
Asthma-related conditions,[b] n (%)			
Allergic rhinitis	37 (100.0)	2527 (96.5)	5554 (95.7)
Atopic dermatitis	17 (45.9)	789 (30.1)	1588 (27.4)
Food allergies	9 (24.3)	690 (26.3)	1659 (28.6)
Patients with serum IgE value,[c] n (%)	37 (100.0)	82 (3.1)	130 (2.2)
Serum IgE, IU/ml, mean ± SD [median] (Q1–Q3, IQR)	1134.45 ± 1730.71 [524] (285–1258, 973)	746.06 ± 1131.26 [293] (70–841, 771)	782.01 ± 1219.73 [319] (90–980, 890)
Patients with FEV_1% predicted value,[d] n (%)	33 (89.2)	1757 (67.1)	4246 (73.1)
FEV_1% predicted, mean ± SD [median] (Q1–Q3, IQR)	84.04 ± 23.77 [83] (68–97, 29)	86.14 ± 18.97 [85] (74–98, 24)	91.52 ± 18.86 [92] (80–103, 23)
Patients with C-ACT score,[d] n (%)	33 (89.2)	1523 (58.1)	4250 (73.2)
C-ACT score, mean ± SD [median] (Q1–Q3, IQR)	15.76 ± 6.03 [14] (10–21, 11)	19.52 ± 5.16 [20] (16–24, 8)	21.69 ± 4.81 [23] (19–26, 7)
Asthma medication use,[e] n (%)			
ICS, any dose	32 (86.5)	1858 (70.9)	2573 (44.3)
Medium-dose ICS/LABA or ICS+LABA	20 (54.1)	970 (37.0)	490 (8.4)
High-dose ICS/LABA or ICS+LABA	14 (37.8)	172 (6.6)	75 (1.3)
LTM	22 (59.5)	1264 (48.2)	1976 (34.0)
OCS	13 (35.1)	548 (20.9)	378 (6.5)

ACT: Asthma Control Test; FEV_1% predicted: forced expiratory volume in 1 s as percentage of predicted value; ICS: inhaled corticosteroids; IQR: interquartile range; LABA: long-acting beta agonists; LTM: leukotriene modifiers; OCS: oral corticosteroids; SD: standard deviation; Q1: first quartile; Q3: third quartile.

[a]Measured as of the index year.

[b]Measured as of the index date based on active problems identified with ICD-9-CM/ICD-10-CM codes.

[c]Measured any time prior to and including the index date; the value closest to the index date is selected.

[d]Measured during the 12-month baseline period prior to and including the index date; the value closest to the index date is selected.

[e]Measured during the 12-month baseline period not including the index date.

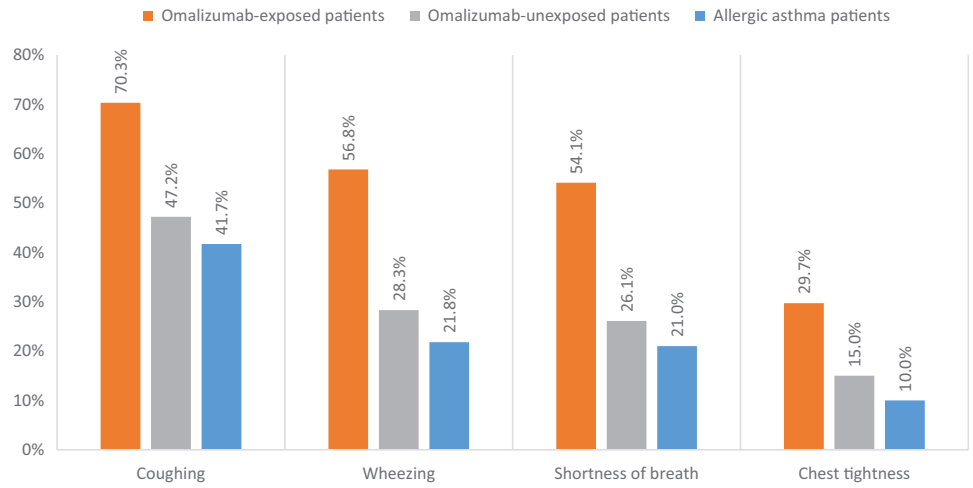

Figure 2. Proportion of patients with asthma-related symptoms during baseline period. Symptoms were identified during the 12-month baseline period prior to and including the index date based on caregiver-reported information or as of the index date based on active problems identified with ICD-9-CM/ICD-10-CM codes.

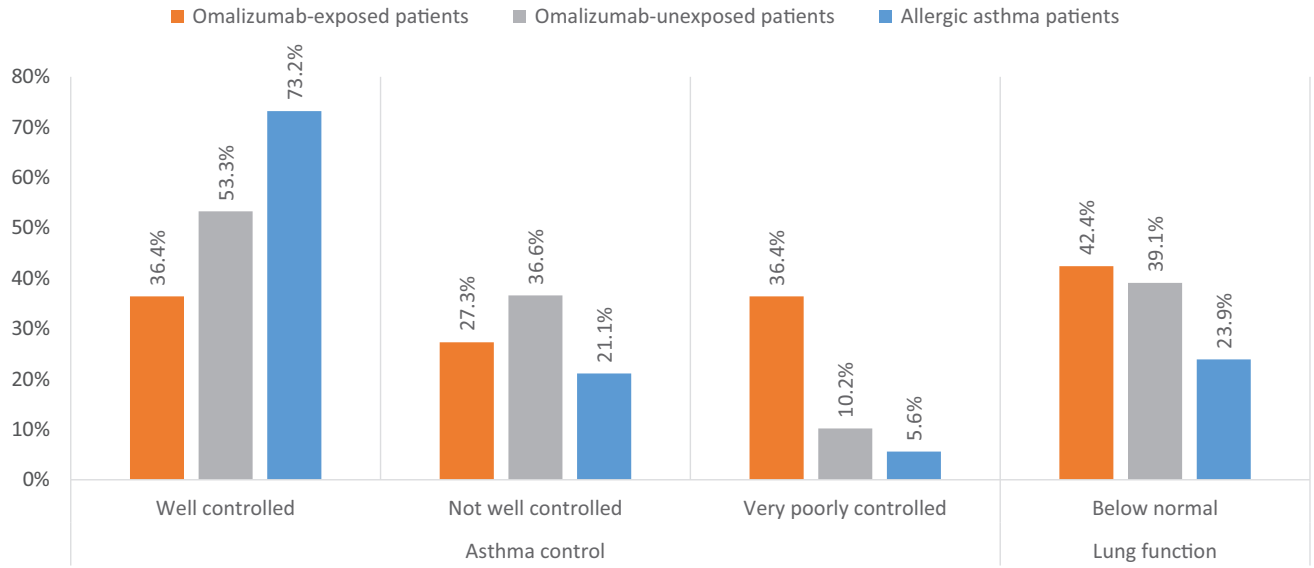

Figure 3. Proportion of patients reaching asthma control and lung function thresholds during baseline period. FEV_1% predicted: forced expiratory volume in 1 s as percentage of predicted value. Asthma control was identified based on the Childhood Asthma Control Test score ($\geq$20 for well controlled; 13–19 for not well controlled; $\leq$12 for very poorly controlled) obtained as of the last assessment during the 12-month baseline period prior to and including the index date. Lung function below normal was defined as FEV_1% predicted $<$80%; FEV_1% predicted value was obtained as of the last assessment during the 12-month baseline period prior to and including the index date.

asthma. Our study is also timely with respect to clinical characteristics of omalizumab-exposed pediatric patients. In Europe, add-on omalizumab therapy in children aged 6–11 years with severe AA has been approved for more than 7 years, allowing to accumulate the real-world experience with the drug.[26–28] In the U.S., information is limited due to the recently expanded indication of omalizumab to pediatrics. Since U.S. omalizumab indications are broader extending to moderate-to-severe patients as opposed to just severe in Europe, findings of this study with respect to the profile of omalizumab-exposed patients could be especially useful for American physicians.

Description of omalizumab-exposed and omalizumab-unexposed uncontrolled moderate-to-severe pediatric AA patients suggested that exposure to omalizumab might correlate with even poorer baseline asthma control and lung function and higher prevalence of symptoms. Higher

total mean IgE level correlated with a more severe baseline disease profile in omalizumab-exposed patients. A higher proportion of patients with Medicaid coverage found among omalizumab-exposed could speak of economic barriers limiting the access to the drug. Economic barriers could explain the difference in severity between omalizumab-exposed and omalizumab-unexposed uncontrolled moderate-to-severe patients, causing the treatment to be postponed until a patient's condition worsens.

In terms of demographics, omalizumab-exposed patients in this study were similar to patients enrolled in clinical trials.[22,23,29] Although, in contrast to two trials that led to omalizumab approval in children, most omalizumab-exposed patients in this study were African Americans, this was consistent with a later trial on omalizumab efficacy in inner-city children, adolescents, and young adults.[29] Omalizumab-exposed African American patients in this study did not display clear signs of being more severe than omalizumab-exposed patients overall based on lung function and asthma control. A larger proportion of African American patients in the omalizumab-exposed cohort in this study should be viewed in the context of a relatively small size of the cohort itself. It may be location driven, since patients might have been treated in areas with a higher prevalence of African American population.

Omalizumab-exposed patients in this study appeared more severe at the baseline and had a higher total IgE compared to patients in clinical trials.[22,23,29] The mean total IgE of 1134.4 IU/ml in the current study was above the range of 348–476 IU/ml reported in clinical trials.[22,23] The mean baseline FEV_1% predicted of 84.0% in this study was at the lower bound of the 84.0%–92.9% range reported in clinical trials.[22,23,29] Similarly, the mean C-ACT score of 15.8 in this study was lower compared to 20.5 reported in a clinical trial.[29] Additionally, omalizumab-exposed patients in this study had higher baseline use of leukotriene modifiers and OCS.[22] These differences in severity and total mean IgE values compared to clinical trials could be expected, since in this study, patients in the omalizumab-exposed cohort received omalizumab off-label, prior to its approval for pediatrics in the U.S., possibly due to their severe condition.

Compared to patients in a relatively large European real-world study, omalizumab-exposed patients in this study appeared slightly less severe based on the asthma control: 63.6% had a C-ACT score <20 compared to 85% of patients with poor asthma control in the European study.[27,28] At the same time, mean FEV_1% predicted at the baseline in the European study was slightly higher (88%), and the prevalence of allergic rhinitis and atopic dermatitis lower compared to the current study.[27] Mean total IgE levels were similar (1125 IU/ml in the European study).[27] Some differences in patient severity between studies could be related to the fact that in Europe omalizumab is indicated in severe patients while in the U.S. the indication also includes patients with moderate disease.

Although this study did not assess outcomes of omalizumab treatment, randomized control trial evidence supported efficacy and safety of omalizumab as an add-on therapy in pediatric patients with moderate-to-severe asthma, and the European real-world experience confirmed these findings in pediatric patients with severe asthma.[30,31] These prior studies demonstrated that in pediatric patients with high disease burden omalizumab can improve asthma control, reduce the incidence and frequency of exacerbations, reduce health care resource utilization including hospitalizations, emergency room and unscheduled office visits, have corticosteroid-sparing effects, and eventually improve the quality of life.[30,31] In the current study, 37.8% of omalizumab-exposed patients received high-dose ICS and 35.1% received OCS at the baseline. Corticosteroid-related adverse events appear to be most common in patients receiving high-dose ICS and concomitant OCS,[32,33] and thus corticosteroid-sparing effects of omalizumab are important outcomes that could translate into fewer adverse events in children. Further studies conducted in the U.S. clinical practice are warranted to supplement this growing evidence of the safety and efficacy profile of omalizumab in pediatric patients.

Study Limitations

First, EMR data contain information on prescriptions ordered but not on prescription filled. A written prescription does not guarantee that medication was dispensed. Matched pharmacy claims were unavailable to analyze dispensed prescriptions. Of note, exposure to omalizumab was defined as either a prescription order or an injection of omalizumab. Second, reasons why OCS were prescribed (chronic daily use or exacerbations control) were unknown. Third, data on the care and prescriptions patients received outside of the Allergy Partners Network were unavailable. Fourth, patient- or caregiver-reported information (e.g., symptoms, answers to the C-ACT questionnaire) might introduce potential recall bias. Fifth, in any database, coding inaccuracies and missing information are possible; however, these errors are not widespread enough to have any substantial impact on the results. Finally, as with all observational studies, the results should be interpreted with due consideration that factors other than treatment of interest have confounded findings. Specifically, omalizumab-exposed patients in this study might be more severe than current-time pediatric omalizumab-exposed patients, as they initiated omalizumab off-label.

Conclusions

This retrospective EMR study suggested that in a real-world setting, pediatric patients with uncontrolled moderate-to-severe AA have a significant disease burden, as shown by high rates of poor lung function, symptoms prevalence, and poor disease control. Omalizumab-exposed patients in this study appeared to have a more severe disease profile compared to omalizumab-unexposed patients and patients involved in omalizumab clinical trials. Currently available treatments could help improve disease management in this population.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Kavati, Ortiz, Paknis, and Vegesna are employees of Novartis Pharmaceuticals Corporation. Stone and Schiffman are employees of Allergy Partners. Pilon, Zhdanava, and Lefebvre are employees of Analysis Group, a consulting company that received research grants from Novartis Pharmaceuticals Corporation.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by Novartis Pharmaceuticals Corporation.

Authors' Note

This study was presented as an electronic poster at the *Annual College of Allergy, Asthma and Immunology* meeting, October 26–30, 2017, Boston, MA.

Ethical Approval

This study was exempted from Institutional Review Board review by the letter from New England IRB.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

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